REMARKS

Claims 44-49, 51-53, 63, 70-79, 83 and 84 are pending in the application. Claims 1-43, 50, 55-57, 62, 65 and 81-82 were cancelled in a prior Amendment and claims 54, 58-61, and 64-69 are cancelled by this Amendment. The claims have been amended to omit the descriptor "synthetic" from all claims using that descriptor. Claims 1 and 63 have been amended to recite the specific types of differentiation-promoting factors for use in contacting the progenitor cells. Support for this Amendment is found at page 6 of the Specification.

I. Objection to Claim 52 - Improper Dependent Form.

At item 2 of Paper No. 16, the Examiner maintains the rejection of claim 52 under 37 C.F.R. 1.75(c) as being of improper dependent form for failing to further limit the subject matter of the previous claim. Applicants continue to traverse this rejection.

Claim 52 is directed to the neuronal tissue of claim 44 wherein such tissue is derived from a single cell. Claim 44 is directed to a neuronal tissue that is derived from a brain or spinal cord **tissue**. As is known to a person of skill in the art, a "tissue" is a collection of single cells, *see* Oxford Dictionary of Biochemistry and Molecular Biology (1997) at 649, attached hereto, and a population of cells may be culture form a single cell or from a collection of cells.

Thus, claim 52 does limit claim 44, as it is drawn to neuronal tissues derived from a single cell of a brain or spinal cord tissue (collection of cells). The Examiner himself makes this point in the Office Action when he states that a brain or spinal cord tissue comprises many types of cells. Accordingly, it is respectfully requested that the Examiner reconsider and withdraw the objection.

II. Rejection Under 35 U.S.C. § 112, First Paragraph - Written Description.

The Examiner has maintained the rejection of claims 44-49, 51-54, 58-61, 63-64, 66-79 and 83-84 under 35 U.S.C. § 112, first paragraph, asserting that these claims contain subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the invention. As basis for the maintenance of these rejections, the Examiner provides scant

information, relying instead on the reasons made of record for claims 26-43 in Paper Nos. 9 and 12. The applicants traverse this rejection.

First, as a threshold matter, the applicants submit that this rejection is not proper, as the Examiner has failed to explain why, with respect to each of the twelve points, the Examiner does not find the applicant's arguments presented in the prior response persuasive. Accordingly, the applicant submits that this is not a proper Office Action, and requests that in the next communication, if such rejection is maintained, that the Examiner provide precise and explicit reasons why each of the applicant's assertions is deemed to be unpersuasive.

With respect to the substantive rejections, as discussed in the prior response, the Examiner argues that there is no written support in the Specification for the following:

(i) "synthetic neuronal tissue,"

(ii) "partially differentiated neuronal progenitor cells that maintain their capability to perform mitosis,"

(iii) ". . . differentiation-promoting factor are contacted for at least two hours,"

(iv) "separated . . . after at least two hours,"

(v) "wherein the factor is an extra cellular matrix of human tissue,"

(vi) "wherein the recipient and the mammal are the same individual,"

(vii) "wherein the single progenitor cell is selected on the basis that it expresses a marker characteristic of the selected type of neuron,"

(viii) "the single neuronal progenitor cell is proliferated by contacting the cell with a mitogen after selecting the cell,"

(ix) "wherein the synthetic tissue does not comprise sufficient glial cells to provoke an immune response . . . recipient,"

(x) "<90% [95%] of cells in the synthetic tissue are the progenitor cells,"

(xi) "partial differentiation is performed more than once," and

(xii) "proliferating the sub-cloned partially-differentiated neuronal progenitor cell." The applicant respectfully traverses these rejections.

With respect to the terms designated items nos. i, iii, iv, v, vi, and vii it is believed that the § 112 rejection is no longer applicable based upon the fact that the claims containing these phrases are cancelled, either in this Amendment or the prior Amendment. Accordingly, the Examiner's express withdrawal of these rejections is requested.

None of the remaining subject matters listed above is new matter under § 112, first paragraph. As discussed in the prior response, there is no *in hac verba* requirement when evaluating written description; it is sufficient that the elements of the claims are supported implicitly or inherently by the Specification. M.P.E.P. 2163.

With respect to the phrase "partially differentiated neuronal progenitor cells that maintain their capability to perform mitosis" (item ii), support is found in the Specification at page 3, lines 12-14, 17-19. ("tissue ... is prepared according to the invention which includes ... partial differentiation *in vitro*.";). As used in the invention "a population of determined neuronal progenitor cells that have been selected and partially differentiated maintains the ability to perform mitosis allowing for performing subsequent proliferation step." Using the Specification as information to be coupled with the knowledge charged to a person of skill in the art, this person would have understood that partially differentiating cells are those which have descended sufficiently far on the differentiation pathway such that they are no longer totipotent, but have not entered into the phrase of terminal differentiation, and as such, remain capable of differentiating into "species" of neuronal tissue cells, such as dopaminergic neurons. See also pages 5-7 of the Specification (describing partial differentiation of neuronal progenitor cells that maintain their ability to mitose).

With respect to the phrase "the single neuronal progenitor cell is proliferated by contacting the cell with the mitogen after selecting the cell" (item VIII), support is found in the Specification at page 9, lines 23-34 to page 10, lines 1-25. In that portion of the Specification, an example is provided in which fetal and adult progenitor cell cultures are expanded (proliferated) by culturing the cells in the presence of mitogens ("supplemented with sufficient concentrations of mitogen;" "the expansion medium may contain mitogens").

The Examiner argues that those portions of the claims reciting "wherein the synthetic tissue does not comprise sufficient glial cells to provoke an immune response... recipient" (item IX) is not supported in the Specification. In fact, the contrary is correct. The Specification, at

page 2, lines 3-12, explains that the cultures (the inventive tissues) do not include cells that give rise to immunogenic glial cells in large enough quantities to induce any detectable immune response.

The Examiner argues that this phrase "is not the same" as cultures that do not include cells that give rise to immunogenic glial cells in large enough quantities to induce any detectable immune response. First, as is clear from a reading of the entire Specification, the applicant has used "culture" throughout to express the population of cells that is the neuronal tissue of the claims. Second, applicant has amended the claims to recite that the neuronal tissue does not comprise sufficient cells that give rise to glial cells to provoke an immune response.

With respect to the phrase "less than 90% [95%] of the cells in the synthetic tissue are the progenitor cells," no such phrase is found in the claims. The claims do recite a neuronal tissue wherein more than 95% of the cells in the tissue are the progenitor cells, but such claim element is fully supported in the Specification at least at page 2, lines 17-18. ("greater than 90%, preferably greater than 95%".)

Finally, the Examiner has maintained the rejection of the claims based upon the lack of written description for the language "partial differentiation is performed more than once" and "proliferating the subcloned partially differentiated neuronal progenitor cell." Support for each of these phrases is provided expressly in the Specification. The "partial differentiation" language is supported at least at page 5, lines 2-16.

For at least these reasons, it is respectfully requested that the Examiner reconsider and withdraw the 35 U.S.C. § 112, first paragraph rejections.

III. Rejection Under 35 U.S.C. § 112, Second Paragraph - Indefiniteness.

The Examiner has maintained the rejection of claims 44-49, 51-54, 58-61, 63-64, 66-79 and 83-84 under 35 U.S.C. § 112, second paragraph, asserting that these claims are indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Specifically, it appears that the Examiner believes that the term "differentiation-promoting factor" is indefinite. The claims have been amended to recite the specific differentiation-promoting factors for use in the composition and process of the invention. Accordingly, the

Examiner's rejection is no longer applicable. Its reconsideration and withdrawal is respectfully requested.

IV. Rejections Under 35 U.S.C. § 102(b) Based Upon U.S. Patent No. 5,411,883 and International Patent Application Publication No. WO 97/02049.

The Examiner has maintained the rejection of claims 44-49, 51-54, and 58-84 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,411,883 of Boss, *et al.* ("Boss") and International Patent Application Publication No. WO 97/02049 of Luskin ("Luskin"), each taken individually.

The Examiner contends that Boss teaches isolation of human and porcine neuron progenitor cells that are "brain-derived neuronal tissue" from the mesencephalon. The Examiner asserts that these cells inherently contain progeny of a single totipotent neural stem cell derived from immature progenitor cells. The Examiner has rejected the applicant's previous arguments, asserting that "no purity limitations etc." are recited in the claims to distinguish them from Boss.

With respect to Luskin, the Examiner has previously asserted that Luskin teaches isolation of human and mammalian brain-derived neuronal progenitor cells capable of differentiating into more than 90% dopaminergic neurons. According to the Examiner, Luskin's progenitor cells contain less than 5%, and even less than 2% glial cells. The Examiner states that "immature progenitor cells" are inherently the progeny of single multi-potent neuronal stem cells. Again, the Examiner argues that applicant's prior arguments are non-persuasive as the claims recite "no purity limitations etc."

The applicant respectfully traverses each of these rejections.

Boss is directed to isolation and culture methods designed to proliferate neuron progenitor cells *in vitro* to produce a culture that differentiates to produce dopamine-producing cells. The cells of the Boss invention either spontaneously differentiate *in vitro*, or can induce to differentiate *in vitro,* producing a population of mature neurons that produce dopamine, prior to implantation into the host. Col. 3, l. 58-60. The Boss neuron progenitor cells are derived from the mesencephalon tissue obtained from a mammalian donor. The Boss cultures are described as being two dimensional monolayers in which differentiating neurons and glial cells can be observed. Col. 6, l. 10-12. It is these cultures (already differentiated into neurons and glial cells)

that are implanted into the host. See *id.*; see col. 13, l. 65-67. Thus the transplantation tissue culture of Boss includes fully differentiated, neuronal progenitor cells that are incapable of undergoing mitosis.

Luskin discloses that the neuronal progenitor cells in the Luskin composition express a neuron-specific marker. However, the progenitor cells can differentiate to become any of a variety of types of neuron cells. Thus, the cells of the Luskin culture are not sufficiently differentiated that they are capable of becoming only substantially one type of neuronal cell, as are the cells of the invention.

Neither Boss nor Luskin anticipates the claimed invention, for neither reference teaches every element of the invention. In particular, the neuronal tissue of the invention consists essentially of partially differentiated neural progenitor cells that maintain their capacity to undergo mitosis and are capable of differentiating into substantially only dopaminergic neurons. In contrast, the tissue cultures of Boss include fully differentiated neurons as well as glial cells. See col. 3, l. 58-60. Similarly, the tissue cultures of the Luskin composition contain cells that are capable of differentiating into a variety of types of neuronal cells. Therefore, since the cultures of the Boss reference contain fully differentiated neuronal cells and glial cells and the compositions of the Luskin reference contain neuronal progenitor cells that can differentiate into cell types other than (or in addition to) dopaminergic neurons, such cultures and compositions are not the same as the claimed neuronal tissue.

Additionally, as articulated in the prior response, the Examiner has not met the legal burden of demonstrating that the cultures of the Boss reference do not contain sufficient cells that give rise to glial cells to provoke an immune response upon implantation. The Examiner has previously argued that this characteristic is inherently present in the Boss disclosure, merely because Boss does not discuss, one way or the other, whether the implanted tissue cultures invoke an immune response. That the reference is silent on this point is not proof that the tissue culture disclosed in Boss necessarily gives rise to a tissue culture from which there are no cells that give rise to glial cells sufficient to provoke an immune response.

Accordingly, for at least the reasons given above, it is respectfully submitted that the disclosures of Boss and Luskin do not teach all elements of the invention, and therefore do not anticipate it. Withdrawal of these rejections is respectfully requested.

CONCLUSION

In view of the foregoing, it is submitted that claims 44-49, 51-53, 63, 70-79, 83 and 84 are distinguished over the cited art and are fully compliant with 35 U.S.C. § 112. Reconsideration and allowance of these claims at the earliest opportunity is respectfully requested.

Respectfully submitted,

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Enclosure: Oxford Dictionary of Biochemical and Molecular Biology (1997) at 649